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IN THE UNITED STATES DISTRICT COURT
DISTRICT OF UTAH CENTRAL DIVISION

BRIGHAM YOUNG UNIVERSITY, a Utah Non-Profit Education Institution; and Dr. DANIEL L. SIMMONS, an individual, Plaintiffs, vs. PFIZER, INC., a Delaware corporation; G.D. SEARLE & COMPANY, a Delaware corporation; G.D. SEARLE LLC, a Delaware limited liability company; MONSANTO COMPANY, a Delaware corporation; and PHARMACIA CORPORATION, a Delaware corporation, Defendants.	Case Number: 2:06-CV-890-TS (BCW) **RESPONSE IN OPPOSITION TO DEFENDANTS' MOTION FOR PARTIAL SUMMARY JUDGMENT REGARDING PLAINTIFFS' COX-1 TRADE SECRET CLAIMS** **(RESPONSE TO DEFENDANTS' MOTION NO. 7)**

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INTRODUCTION

It is undisputed that, in its research leading to the discovery of Celebrex, the only mouse COX-1 cDNA clone Monsanto ever used was the one it received from Dr. Simmons; indeed, Monsanto's Dr. Seibert testified she didn't know of any other source for a mouse COX-1 clone in 1991, 1992 or 1993.[1] So the fact that a single scientist, David DeWitt, claimed in a 1990 publication to have a mouse COX-1 clone hardly means that Dr. Simmons's mouse COX-1 cDNA was "publicly available," anymore than Dr. Simmons's discovery of a mouse COX-2 clone in 1991 meant that a COX-2 clone was then "publicly available." In fact, Pfizer offers no evidence that Dr. DeWitt made his mouse COX clone available to anyone, let alone made it publicly available.

More importantly, Pfizer never claims that Dr. DeWitt made his clone available to Monsanto. And as the Eighth Circuit only recently reiterated, "it is no defense to claim that one's product **could have been** developed independently," if in fact it was taken from the plaintiffs.[2]

Furthermore, that DeWitt published what he said was the *DNA sequence* of his COX-1 clone did not make the *clone itself* "readily available." Although a skilled scientist at that time may have been able to make a clone from a DNA sequence, making a clone is a difficult process, fraught with problems.[3] Pfizer certainly knows this, because it took Monsanto itself over a year to construct a human COX-2 clone, even though Monsanto not only had the publicly-available DNA sequence for that clone, had an actual human COX-2 clone from Dr. Tim Hla to use as a

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[1] Statement of Facts ("SOF") ¶¶ 12-14.

[2] *AvidAir Helicopter Supply, Inc. v. Rolls-Royce Corp.,* 2011 U.S. App. LEXIS 24620, *13 (8th Cir. Sept. 20, 2011) (internal quotation marks and citation omitted; emphasis added).

[3] SOF ¶¶ 19-62.

guide and molecular probe, and had also mobilized 50 molecular and cell biologists to carry out project, knowing it was in a "race" to be the first to market a COX-2 selective drug.[4] Moreover, the mere publication of a DNA sequence does not mean the published sequence was correct, because sequencing itself is difficult, and errors are common, including errors in published material.[5]

Pfizer's argument also overlooks that fact that Dr. Simmons's mouse COX-1 clone was part of the only pair of COX-1 and COX-2 clones in the world cloned in the same species;[6] together, those clones had independent economic value and constituted a combination or compilation trade secret.

Finally, as Pfizer's own arguments in this case make clear, clones are not fungible. One of Pfizer's central arguments in this case is that Dr. Simmons's COX-2 clone didn't work, so that—as Pfizer claims—Monsanto had to use Dr. Herschman's COX-2 clone instead. While BYU hotly disputes that, BYU agrees that all clones are not created equal. And when Monsanto received from Dr. Simmons a mouse COX-1 cDNA clone that Monsanto determined to be "useful," it had a unique asset of far greater value than the published "steps and techniques" for making a clone.[7]

For these reasons and others discussed below, Pfizer's motion is not well taken and should be denied.

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[4] SOF ¶¶ 45-53.
[5] SOF ¶¶ 19-44.
[6] SOF ¶¶ 9-10.
[7] SOF ¶ 17.

BYU'S RESPONSE TO PFIZER'S STATEMENT OF FACTS

Pfizer's Statements of Fact:

A. Plaintiffs' Trade Secret Contentions Regarding Mouse COX-1 Materials and Information.

1. Plaintiffs' response to Defendants' contention interrogatory regarding trade secret misappropriation identifies dozens of alleged "trade secrets" that they contend have been misappropriated by the Defendants, including: (a) the mouse COX-1 DNA and amino acid sequences; (b) the restriction map for the mouse COX-1 DNA sequence; and (c) a mouse COX-1 cDNA clone. (Russell Decl., Ex. 5 (Plaintiffs' amended second supplemental response to interrogatory no. 8) at 33-34.) 22

BYU Response:

Plaintiffs admit the above, with the clarification that the misappropriated sequences relate to the unique DNA and amino acid sequences to Dr. Simmons's mouse COX-1 cDNA clone in the bluescript sk- vector, which Dr. Simmons designated the "M4A1 plasmid."

2. Plaintiffs allege that "On April 29, 1991, D r. Simmons provided Monsanto with his murine (mouse) COX-1 and COX-2 clones (Dkt. No. 445 at ¶ 69; see also Russell Decl., Ex. 9 (April 29, 1991 Letter from Daniel Simmons at BYU to Karen Seibert and Jaime Masferrer at Washington University).)

BYU Response:

Plaintiffs admit the above, with the clarification that the COX-1 and COX-2 clones supplied were both in the bluescript sk- vector, the COX-1 cDNA being the "M4A1 plasmid," and the COX-2 cDNA clone being the "C75" plasmid.

3. Plaintiffs allege that on July 16, 1991, "BYU faxed amino acid comparisons for COX 1 and COX 2 to Monsanto." (Dkt. No. 445 at ¶ 458; see also Russell Decl., Ex. 11 at p. 2 (Fax from BYU to Washington University).)

BYU Response:

Plaintiffs admit this fact.

4. Plaintiffs' interrogatory response also indicates that they provided the DNA sequence for mouse COX-1. (Russell Decl., Ex. 5 at 33-34; see also Russell Decl., Ex. 11 at pp. 3-5 (Fax from BYU to Washington University).)

BYU Response:

Plaintiffs admit this fact, with the clarification that the DNA sequence provided was not the full sequence for Dr. Simmons's M4A1 plasmid, but only the GenBank DNA sequence for the "coding region" of COX-1.

B. Facts Regarding The Public Disclosure And Availability Of The Mouse Cox-1 DNA And Amino Acid Sequences.

5. On or about March 25, 1990, an article entitled "The Aspirin and Heine-binding Sites of Ovine and Murine Prostaglandin Endoperoxide Synthases" by David L. DeWitt, et al. (hereinafter, "the DeWitt Paper"), was published in the Journal of Biological Chemistry. (Russell Decl., Ex. 21 (DeWirt, et al., *The Aspirin and Heme-binding Sites of Ovine and Murine Prostaglandin Endoperoxide Synthases*, J. Biol, Chem., vol. 265, pp. 5192-5198, 1990) at p. 1.)

BYU's Response:

BYU admits this fact.

6. Figure 4 of the DeWitt Paper discloses the "Nucleotide and deduced amino acid sequence (standard *one-letter* symbols) of a cDNA coding for a mouse 3T3 cell PGG/H

synthase." (*Id*. at FIG. 4.) The "cDNA coding for a mouse 3T3 cell PGG/H synthase" refers to a cDNA for what is now known as mouse COX-1.

BYU's Response:

BYU admits that this is what the DeWitt article says.

7. In a 1991 publication entitled "Multiple Cyclooxygenases: Cloning of a Mitogen-Inducible Form," authored by Dr. Simmons and other members of his laboratory, the authors recognized that the DeWitt Paper disclosed the clone for what is now known as mouse COX-1. (Russell Decl., Ex. 22 at 67.) "The sheep seminal vesicle cDNAs have been used to clone the homologous gene in human (5) and mouse (3)." (*Id*.) Item number (3) is the DeWitt paper.

BYU's Response:

BYU admits that the publication says what is quoted above, but denies that the DeWitt paper "disclosed the clone" for what is now known as COX-1.

8. BYU's 30(b)(6) witness testified that the mouse COX-1 DNA sequence that BYU provided in June 1991 was obtained from GenBank (a publicly available database for DNA and amino acid sequences), and that the GenBank sequence was the same as the Dewitt sequence:

> Q. Okay. Can you tell me how this sequence on Pages 3 through 5 of Exhibit 272 compares to the DeWitt sequence, Exhibit 1076?
>
> A. My understanding is that the MOUPGHS [mouse COX-I] sequence that's listed here was obtained from Gen Bank, which is the De Witt sequence.

(Russell Decl., Ex. 46 (BYU 30(b)(6) deposition) at 197:19-24 (emphasis added).)

BYU Response:

BYU admits that the deposition testimony is as quoted, but as previously stated, the sequence was limited to the coding region.

C. Facts Regarding the Public Disclosure And Availability of The Mouse Cox-1 Clone.

9. In addition to the mouse COX-1 clone that BYU alleges was provided to Monsanto, BYU also licensed and provided its mouse COX-1 clone to a company called Oxford Biomedical Research, Inc. ("Oxford"). (See Russell Decl., Ex. 10 (BYU/Oxford license agreement).)

BYU's Response:

BYU denies this statement, which the referenced license agreement doesn't support. As the license agreement states, BYU only licensed Oxford to use BYU's COX-1 cDNA for the sale of "probes," and not for "diagnostic or therapeutic uses of the cDNAs." As Dr. Callewaert, who signed the agreement for Oxford, acknowledged, Oxford was never licensed to sell the complete cDNA of COX-1 or COX-2, but just probes.[8] As Pfizer expert Dr. Mancini acknowledged, a "probe" is just a "small section" of the cDNA, and if you bought such a probe from Oxford, it had limited use, because you didn't know where in the cDNA the probe was taken from, and you didn't know the sequence for the probe.[9]

10. The BYU/Oxford license agreement describes the mouse COX-1 clone provided by BYU to Oxford as follows: "A cDNA clone of routine prostaglandin G/H synthase (hereafter

[8] D. Callewaert Dep., 19 Oct 10, Ex. 238 at 151:11-16.
[9] J. Mancini Dep., 7 Nov 11, Ex. 32 at 248:18-250:9.

PGHS) which is the same nucleic acid sequence published by DeWitt et. al. J. Biol. Chem. 265:5192-5198." (Id. at Appendix A (emphasis added).)

BYU's Response:

BYU admits that the document is accurately quoted, though in fact the statement is only true for the coding region of the COX-1 clone..

11. Dr. Lynn Astle, the head of BYU's Technology Transfer Office in 1991 and a Ph.D. in biochemistry, testified that the biological material identified in Appendix A to BYU's license with Oxford were the same as the biological material allegedly provided to Defendants in April 1991:

> Q. And this Appendix A, the biological material, that's the same material that's reflected in Exhibit 12, is it not?
>
> A. In Exhibit 12? What was Exhibit 12?
>
> Q. The letter from Doctor Simmons to Doctor Seibert sending that sending the University of Washington some biological material?
>
> A. Okay. Yes, I believe it was.

(Russell Decl., Ex. 51 (Astle deposition testimony) at 183:18-25.)

BYU's Response:

BYU admits that Pfizer quoted Dr. Astle's deposition testimony correctly..

12. The enclosure letter from BYU to Oxford confirms that the mouse COX-1 clone provided to Oxford was the same as the mouse COX-1 clone provided to Drs. Seibert and Masferrer in April 1991. (Compare Russell Decl., Ex. 12 (Sept. 12, 1991 l etter from Dr. Simmons to Oxford; "Please find in this shipment three aliquots of my cyclooxygenase clones...The M4A1 clone contains the murine [mouse] homolog of the original sheep seminal

vesicle form isolated by DeWitt and Smith and others.") with Russell Decl., Ex. 9 (April 29, 1991 Letter from Dr. Simmons to Drs. Seibert and Masferrer; "Enclosed please find aliquots of the murine COX- 1 and COX-2 in Bluescript sk-."; "1.) Murine COX-1 is encoded by the M4A1 plasmid.").)

BYU's Response:

BYU admits this fact, but again notes that Oxford was only authorized to use the COX-1 clone to sell probes, not the full cDNA clone itself.

13. The DeWitt Paper provides an explanation of the techniques that he and his colleagues used to obtain their mouse COX-1 cDNA clone. (See Russell Decl., Ex. 21 at 5193 ("EXPERIMENTAL PROCEDURES"; "Cloning and Sequencing of a Mouse 3T3 Cell cDNA for PGG/H Synthase").)

BYU's Response:

BYU admits that the DeWitt paper gives a general explanation of the techniques they used to obtain their mouse COX-2 cDNA clone.

14. According to the 1989 textbook Molecular Cloning: A Laboratory Manual, "[A]s a consequence of a wide range of technical and theoretical advances, cDNA cloning is now well within the range of any competent laboratory." (Russell Decl., Ex. 19 at 8.3.) The Molecular Cloning textbook describes many different cDNA cloning protocols and methods. (See, e.g., id. at 8.36-8.45; 8.53-8.63.)

BYU's Response:

BYU assumes that Pfizer has accurately quoted the referenced textbook.

D. Facts Regarding the Public Disclosure And Availability Of The Mouse Cox-1 Restriction Map.

15. Figure 1 of the DeWitt Paper discloses a "[r]estriction map for a mouse cDNA for PGG/H synthase." (Russell Decl., Ex. 21 at 5193.) The DeWitt restriction map shows cutting sites for four different restriction enzymes: EcoRl, SacI, Pstl, and Xbal.

BYU's Response:

BYU admits this fact, but notes that the restriction map for Dr. Simmons's COX-1 cDNA was different than the one disclosed in Dr. DeWitt's paper..

16. By 1984, at least the University of Wisconsin Genetics Computer Group (UWGCG) had created a computer program that could generate a restriction map for a DNA sequence. (See Russell Decl., Ex. 24 (Devereux J., et al., A Comprehensive Set of Sequence Analysis Programs for the VAX, Nucleic Acid Res. P. 12:387-95,388 (1984)).) The computer program included "mapping and searching" functionality that could be used to "display all of the cuts for each restriction enzyme" for a given sequence. (Id. at 388.)

BYU's Response:

BYU admits that the referenced paper so states.

BYU'S STATEMENT OF FACTS[10]

A. Dr. Simmons Shared With Monsanto His Unique COX-1 cDNA, Restriction Map, and Nucleotide And Amino Acid Sequence.

1. On 29 April 1991, Dr. Simmons sent Monsanto various confidential biological materials and information, including his "murine" or mouse COX-1 and COX-2 cDNAs in

[10] All exhibits in support of this Opposition have been consolidated with Plaintiffs' exhibits in support of concurrently filed oppositions.

"Bluescript sk-."[11] The Court has previously ruled that these materials and information were subject to the confidentiality provisions of the Research Agreement, even though sent prior to the effective date of that agreement.[12]

2. Under ¶ 4.1 of the Research Agreement, Monsanto agreed that BYU's "Confidential Information" would "be used only as provided for in this Agreement," and further agreed to hold such information "in confidence," to limit its disclosure "to those personnel who need such access for purposes of this cooperative effort," and also agreed "not to duplicate or use" the information in "any other manner…"[13]

3. The Research Agreement defined "Confidential Information" to include:

> proprietary information, including information relating to transformed cells, genes, transformation vectors, transformation, selection and regeneration procedures, media formulations, chemicals, DNA sequences and probes…[14]

4. "Bluescript sk-" is a type of biological "vector" that holds the cDNA.[15] The biological construct comprised of Dr. Simmons's COX-1 cDNA inserted in the Bluescript sk- vector was a unique complex molecule, and Dr. Simmons's lab gave it a unique identifier, naming it the "M4A1" plasmid."[16]

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[11] Ltr. to K. Seibert and J. Masferrer from D. Simmons, 29 Apr 91, BYU-PFE 059332, Ex. 15.
[12] Memorandum Decision and Order, 30 Sep 09, Dkt. 302 at 7.
[13] Research Agreement, 1 Aug 91, ¶ 4.1, BYU-11-0111-127, Ex. 9.
[14] *Id.*
[15] D. Simmons Rebuttal Expert Rpt., 26 Aug 11, ¶ 95, Ex. 161.
[16] D. Simmons Amended and Supp. Expert Rpt., 10 Jun 11, ¶ 317, Ex. 57.

5. The construct comprised of Dr. Simmons's COX-2 cDNA inserted in the Bluescript sk- vector was another unique complex molecule, and Dr. Simmons's lab gave it a unique identifier, naming it the "C75" plasmid.[17]

6. Dr. Simmons included with his 29 April 1991 letter special instructions on how to use the COX-1 M4A1 plasmid to produce COX-1 mRNA:

> To transcribe it to produce COX-1 mRNA, linearize the plasmid with BAMHI and polymerize with T7 RNA polymerase. For anti sense RNA, linearize with Hind III and polymerize with T3 polymerase. To cut out the full-length insert for random labeling use BAM HI and HIND III.[18]

7. Dr. Simmons later provided Monsanto with the full nucleotide sequence of his M4A1 COX-1 cDNA, along with a restriction map for that construct.[19] A "restriction map" gives detailed instructions that molecular biologists use to work with cDNAs.

8. The full nucleotide sequence of Dr. Simmons's mCOX-1 cDNA was comprised of 2,335 base pairs.[20] This differed from the full nucleotide sequence of the mCOX-1 clone constructed by Dr. DeWitt, which was 2,757 base pairs.[21] According to BYU expert Dr. Fraser, the mouse COX-1 cDNA clone that Dr. Simmons provided to Monsanto:

> contains the same consensus sequence found in GenBank except that it begins and ends at different points and has a one nucleotide difference in the 3' prime untranslated region. Dr. DeWitt's COX-

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[17] *Id.* at ¶ 312.

[18] Ltr. to K. Seibert and J. Masferrer from D. Simmons, 29 Apr 91, Ex. 15 at BYU-PFE 059332.

[19] D. Simmons Rebuttal Expert Rpt., 26 Aug 11, Ex. 161 at ¶ 95.

[20] E. Harding Searle Notebook No. GDS-11912 at p. 116, 15 Mar 00, at p. 116, BYU-PFE-LNB-E 1000345056, Ex. 137.

[21] DeWitt, et al., *The Aspirin and Heme-binding Sites of Ovine and Murine Prostaglandin Endoperoxide Synthases*, 3 Aug 89, J. Biol. Chem., Vol. 265, No. 9, pp. 5192-5198 at 5196 (1990), Ex. 123.

> 1 clone is different from the consensus sequence in GenBank by two nucleotides and is also different from Dr. Simmons's mouse COX-1 clone sequence by the same two nucleotides.[22]

The nucleotide sequence of what molecular biologists call the "coding region" of Dr. Simmons's mCOX-1 clone, however, was identical to the nucleotide sequence of the coding region of the DeWitt mCOX-1 clone.[23]

9. At the time Dr. Simmons provided these constructs to Monsanto, his mCOX-1 and mCOX-2 cDNAs were the only set of paired mammalian COX-1 and COX-2 clones in the world, an "incredibly valuable resource because they held the key to screening for an NSAID that would selectively inhibit COX-2 over COX-1."[24]

10. Dr. Seibert admits that she knew of no other source for paired COX-1 and COX-2 clones or COX-2 specific antibodies:

> Q. [A]s of April 29, 1991, did you know anybody else in the world who had **paired cDNA clones of COX-1 and COX-2**, other than Dr. Simmons?
>
> A. **No**.
>
> Q. You knew – did you know of anybody in the world as of April 29, 1991, who had **antibodies to COX-2**, other than Dr. Simmons?
>
> * * *

[22] M. Fraser Rebuttal Expert Rpt., 26 Aug 11, p. 4, Ex. 239.

[23] M. Fraser Dep., 27 Oct 11, 191:25-192:9, Ex. 163.

[24] D. Simmons Dep., 20-21 Apr 09, 262:19-263:1, Ex. 1; D. Simmons Decl., 1 Jun 09, ¶ 10, Ex. 12.

A. **That's the only antisera that I was aware of**, I believe, at the time that was hopefully selective for the COX-2.[25]

B. <u>Dr. Simmons's mCOX-1 Clone Was The Only mCOX-1 Clone Monsanto Used, And Monsanto Knew Of No Publically Available Source For An mCOX-1 cDNA</u>.

11. Pfizer's statement of facts does not assert that Dr. DeWitt shared his mCOX-1 clone with anyone, or that Dr. DeWitt was willing to share his mCOX-1 clone with anyone.[26]

12. Monsanto's Dr. Seibert has admitted that the only mCOX-1 clone Monsanto ever used was the one she received from Dr. Simmons on 29 April 1991.[27]

13. Dr. Seibert has also admitted that in 1991, she was unaware of any publicly-available source for a mouse COX-1 cDNA:

Q. (By Mr. Williams) In 1991, do you know a publicly available source of -- did you know of a publicly available source of mouse COX-1 cDNA?

MR. O'MALLEY: Objection to the form. You may answer.

A. I don't -- I don't recall.

Q. (By Mr. Williams) You don't recall –

A. I –

Q. -- any publicly available source?

MR. O'MALLEY: Objection to the form of the question. You may answer.

A. I don't recall any -- any source.[28]

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[25] K. Seibert Dep., 1-3 Jun 10, 359:23-360:14. Ex. 3; Dr. Currie also testified that, in the fall of 1991, he didn't know of anyone other than Dr. Simmons that had a COX-2 specific antibody (M. Currie Dep., 8 Oct 10, 189:11-22, Ex. 49).

[26] Pfizer's Mem. in Supp. of Mot. for Summary Judgment regarding Pls. COX-1 Trade Secret Claims, Statement of Facts, ¶¶ 1-16.

[27] K. Seibert Dep., 1-3 Jun 2010, Ex. 3 at 417:17-418:9.

14. Dr. Seibert also testified that she couldn't recall any "publicly availably source" for mouse COX-1 in 1992 or 1993 either.[29]

15. Pfizer's expert witness, Dr. Mancini, testified that the only other source of mouse COX-1 he could recall in the 1991 to 1993 time period was Dave DeWitt, and Dr. Mancini admitted that he had "no idea" whether Dr. DeWitt would have given that out to anyone.[30]

16. Dr. Mancini also testified that, when he worked at Merck, he didn't think Merck ever shared its COX "clones or other reagents" with its competitors—whether or not published sequences existed for the reagents—and that he himself was prohibited from giving out the COX clones that Merck developed.[31]

17. By no later than 24 March 1992, Monsanto found Dr. Simmons's mCOX-1 clone to have been "useful."[32] Monsanto later used that mCOX-1 clone to develop its recombinant enzyme assay.[33] And as Monsanto represented to regulators in Sweden in applying for a patent

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[28] *Id.* at 418:10-22; *see also* 417:17-419:16.

[29] *Id.* at 418:23-419:16.

[30] J. Mancini Dep., 7 Nov 11, Ex. 32 at 251:16-154:16.

[31] *Id.* at 151:3-152:3.

[32] *Id.* at 522:19-25; Email to P. Needleman from K. Seibert, 24 Mar 91, S00663784-785, Ex. 42.

[33] R. Bell Dep., 29 Sep 11, 126:14-127:13, Ex. 138 (Monsanto used Dr. Simmons's mCOX-1 clone "to express recombinant mouse COX-1"); Cyclooxygenase-2 Inhibitor Project, 9 Sep 02, BYU-PFE 042354 at 356, Ex. 139 ("cDNAs for mouse COX-1 and COX-2 have been obtained and transiently expressed in COS cells…Current efforts are aimed at obtaining efficient high yield expression of mouse COX-2 and COX-1, either in insect cells or by stable expression in mammalian cells"); K. Seibert et al., *Pharmacological and biochemical demonstration of the role of cyclooxygenase 2 in inflammation and pain*, Proc. Natl. Acad. Sci., Vol. 91, pp. 12013-12017 (Dec. 1994), Needle-P 10000004824-828 at 825,827, Ex. 140 ("The coding regions of mouse COX-1 and COX-2 were subcloned in the baculovirus expression vector pVL1393"; "murine and human COX-1 and COX-2 were cloned and expressed in insect cells utilizing a baculovirus expression system, and the relative ability to inhibit the recombinant enzyme *in vitro* was examined"); Queeny Award Nomination Packet, 17 Sep 99, BYU-PFE 651599-675 at 627,

on Celebrex in that country, "**the recombinant enzyme assay provides the only means for assessing the activity of compounds such as celecoxib** under well defined, identical conditions.[34]

18. Dr. Seibert believed that, because of the termination of the Research Agreement, Monsanto needed to find a replacement for Dr. Simmons's mouse COX-1 clone, though Monsanto never did so.[35]

C. Because DNA Cloning and Sequencing Is Difficult And Fraught With Error, The Fact That A Mouse COX-1 DNA Sequence Appears In One Publication Does Not Mean The Correct Sequence Is Now Agreed-Upon And "Publicly Available."

19. As Pfizer's memorandum notes, DNA, a type of nucleic acid, contains individual genes, each of which is comprised of a unique combination of nucleotide "bases"; the particular sequence of those nucleotide bases "determines what type of protein will ultimately be made from a gene." Pfizer Mem. at iii.

1. How cDNA clones are made.

20. In the early 1990s, two general methods were used for cDNA cloning, the "cDNA library" method, and the polymerase chain reaction or "PCR" method.[36]

Ex. 88 ("after cloning and expression of the COX isozymes by the molecular biology group in Monsanto, [Dr. Seibert's] laboratory developed the *in vitro* recombinant enzyme based screening assay that provided all of the basic structure activity data for Searle's COX-2 inhibitors. Thus, Karen was key to developing the system that would define selectivity and ultimately select celecoxib as the lead compound").

[34] Swedish Patent Application – Sponsor's Comment re Primary Pharmacodynamics, Isakso-P 1000015704-707, Ex. 141.

[35] Email to P. Needleman from K. Seibert, 24 Mar 91, S00663784-785, Ex. 42 (stating that she and Dr. Masferrer "feel no impact of severing the relationship with Simmons. The only useful thing either of us ever got from Simmons was the mouse 1 and 2 clones **which were offered to me by Harvey Herschman at the Keystone meeting anyhow**." (emphasis added.)

21. In the first method, a "cDNA library" is constructed from "messenger RNAs" ("mRNAs") extracted from a cellular source.[37] Then, using a biological "probe" that was able to chemically recognize the cDNA of interest, the library was screened to isolate the desired cDNA.[38] The identity of the cDNA must then be confirmed by DNA sequencing.[39]

22. This is the method Dr. DeWitt used to clone his mCOX-1 cDNA in the article cited by Pfizer.[40]

23. The second method of cDNA cloning is to use PCR to "amplify" a cDNA.[41] In that method, small synthetic pieces of DNA (called "oligonucleotides" or "primers") are used to "prime" the synthesis of a cDNA by repeated rounds of "amplification" (replication).[42] Using the PCR amplification method requires significant foreknowledge of the amino acid or nucleic acid sequence of the gene to be cloned, because that knowledge is used to make the primers.[43]

24. Regardless of which method is used, however, the "obtaining of a correct cDNA is fraught with error…."[44] In fact:

> both processes can yield cDNA sequences that represent 1) **variants** of mRNAs in cells, 2) **improperly** or alternatively

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[36] Second Decl. of D. Simmons, *Cromlish v. Young*, 20 Jan 01, ¶ 6, BYU-09-1879-885, Ex. 122.
[37] *Id.*
[38] *Id.*
[39] *Id.*
[40] DeWitt, et al., *The Aspirin and Heme-binding Sites of Ovine and Murine Prostaglandin Endoperoxide Synthases*, 3 Aug 89, J. Biol. Chem., Vol. 265, No. 9, pp. 5192-5198 (1990), Ex. 123.
[41] Second Decl. of D. Simmons, *Cromlish v. Young*, 20 Jan 01, Ex. 122 at ¶ 7, BYU-09-1881-882.
[42] *Id.*
[43] *Id.*
[44] *Id.* ¶ 11, BYU-09-1883-884.

> **processed RNAs**, or 3) **sequences that are in error** through a variety of events that occur during the process of cloning and sequencing, or through improper reading or recording of the cDNA sequence.[45]

25. Moreover:

> The fact that a cDNA clone might contain sequencing errors was well known in 1992 and many examples of the above occurrences existed in the cDNA literature in general as well as in the cyclooxygenase field.[46]

26. Two notable examples involved Dr. DeWitt himself. In 1988, the cDNA cloning of sheep COX-1 was reported in published articles by two different laboratories, that of Merlie and that of DeWitt and Smith.[47] But the sequences reported by the two labs "had multiple nucleotide differences."[48] And as it turned out, the published DeWitt and Smith nucleotide sequence for sheep COX-1 "predicted a protein that potentially is non-functional."[49]

27. Then in 1990, Dr. DeWitt, along with Pfizer-expert Dr. Tim Hla and five other scientists, published a paper comparing the amino acid sequence of a partial human COX clone that Dr. Hla had generated in his laboratory, to that same sequence as reported in the publicly-

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[45] *Id.*

[46] *Id.*

[47] Merlie, et al., *Isolation and Characterization of the Complementary DNA for Sheep Seminal Vesicle Prostaglandin Endoperoxide Synthase (Cyclooxygenase)*, J. Biol. Chem., Vol. 263, pp. 3550-3553 (1988), BYU-PFE 098864-867, Ex. 124; DeWitt, et al., *Primary Structure of Prostaglandin G/H Synthase from Sheep Vesicular Gland Determined from the Complementary DNA Sequence*, Proc. Nat'l Acad. Sci. USA, Vol. 85, pp. 1412-1416 (1988), BYU-UR 000009808-812, Ex. 125.

[48] Second Decl. of D. Simmons, *Cromlish v. Young*, 20 Jan 01, Ex. 122 at ¶ 11, BYU-09-1883-884.

[49] *Id.*

available GenBank database.[50] As Dr. Hla testified, there were 12 errors, or at least differences, between the GenBank human COX amino acid sequence and the amino acid sequence of Dr. Hla's partial human COX-clone.[51] As Dr. Hla also testified about the differences,

> They could be errors, they could be mutations, they could be a little specific differences, there could be -- yeah, **it could be a number of possibilities, but errors is one of the possibility** [sic].[52]

2. <u>The Merck Frosst/University of Rochester dispute over the patent for human COX-2 shows the difficulty of DNA sequencing</u>.

28. The difficulty of determining the correct nucleotide sequence of a COX cDNA during the early 1990s was recognized in a decision in a patent interference action between several scientists at Merck Frosst (Cromlish, Kennedy, O'Neill, Vickers, Wong and Mancini), and scientists at the University of Rochester (Young, O'Banion, and Winn), USPTO Patent Interference No. 104,289 (the "Cromlish Interference").[53] The Cromlish Interference

> relate[d] generally to nucleic acid molecules which encode human COX-2 and can produce or "express" human COX-2 for use in assays for identifying potential COX-2 selective inhibitors.[54]

29. Specifically, scientists at the University of Rochester and at Merck Frosst had both applied for patents on a human COX-2 cDNA clone, but the human COX-2 nucleotide sequence set forth in their patent applications differed from the nucleotide sequence for that gene

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[50] T. Hla Dep., 21 Sep 11, 59:10-63:12, Ex. 126. "Genbank" is a genetic sequence database maintained by the National Institute of Health ("NIH"). *See* www.ncbi.nlm.nih.gov/genbank/.

[51] *Id.*

[52] *Id.* (emphasis added).

[53] Mem. Opinion and Order, 29 Mar 02, *Cromlish v. Young*, pp. 18-20, BYU-02-1653-673, Ex. 127.

[54] *Id.* at p. 3.

that had been previously published by (current Pfizer expert) Dr. Tim Hla.[55] Nevertheless, the Merck Frosst scientists were eventually issued a patent on their human COX-2 cDNA.

30. Because current-Pfizer expert Dr. Joseph Mancini was one of the inventors on that Merck Frosst human COX-2 patent, he was one of the parties in the Cromlish Interference.[56] Dr. Mancini and the other Merck Frosst inventors engaged Dr. Simmons as an expert witness in that case on their behalf.[57] Dr. Simmons then submitted two Declarations that were considered and relied on by the Board of Patent Appeals in issuing its opinion.[58]

31. As Dr. Simmons noted in his Second Declaration in that case, the COX-2 cDNA sequences contained in the Young (University of Rochester) patent applications, as well as those in the Cromlish (Merck Frosst) patent, "were obtained by PCR amplification using primers that were synthesized based on the sequence of a human COX-2 cDNA published by Timothy Hla" in August of 1992.[59] However—despite the competing human COX-2 cDNAs having been derived from Hla's human COX-2 sequence—the nucleotide sequences for their resulting cDNA clones: 1) differed from Dr. Hla's published sequence; and 2) differed from each other.[60]

32. Later, the Young parties (University of Rochester) filed a patent application that "corrected" the human COX-2 nucleotide sequence, and acknowledged that the prior application

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[55] *Id.* at 7-9; 18-19; 28-29.

[56] J. Mancini Dep., 7 Nov 11, Ex. 32 at 158:18-159:12.

[57] *Id.* at 159:18-162:19; Mem. Opinion and Order, 29 Mar 02, *Cromlish v. Young*, Ex. 127 at p. 18.

[58] Decl. of D. Simmons, *Cromlish v. Young*, 28 Sep 00, BYU-09-1852-868, Ex. 128; Second Decl. of D. Simmons, *Cromlish v. Young*, 20 Jan 01, Ex. 122 at BYU-09-1871.

[59] Second Decl. of D. Simmons, *Cromlish v. Young*, 20 Jan 01, Ex. 122 at ¶ 7, BYU-09-1881-882.

[60] *Id.* at ¶ 11, BYU-09-1856.

"does contain errors, and therefore, it is not correct."[61] One issue in the case was whether, taken together, the Young patent applications "disclose[d] an isolated DNA sequence encoding human COX-2."[62]

33. Relying on the testimony of Dr. Simmons, the Board of Patent Appeals held:

> We find the testimony of Daniel L. Simmons on behalf of party Cromlish that **obtaining the correct cDNA sequence** (and amino acid sequence) encoding human COX-2 **is fraught with difficulty** to be highly credible.[63]

34. The Board of Patent Appeals also "**decline[d]**"

> Young's **invitation to assume that the amino acid sequence of Young '364 and '456 Figure 7 is correct,** while the nucleic acid sequence of their Figure 6 is incorrect because the amino acid sequence of Figure 6 "agrees" with that of Hla.[64]

35. As the Board explained:

> Young has **not pointed us to persuasive evidence** of record **that** as of the filing date of Young '365 **the sequences of Hla were accepted as the correct amino acid and nucleic acid sequences** of human COX-2, i.e., that there was the equivalent of a microscope with which to see the sequences of Young '364 and '456 Figures 6 and 7.[65]

36. "Moreover," the Board said, even Young's own expert witness, David Jones, testified that

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[61] Mem. Opinion and Order, 29 Mar 02, *Cromlish v. Young*, Ex. 127 at pp. 8, 18.
[62] *Id.* at p. *17.*
[63] *Id.* at p. 18.
[64] *Id.* at p. 19.
[65] *Id.*

> he did not know what the "correct" sequence for human COX-2 was—simply that the sequences from his own group, Hla, Young and Cromlish were "different."[66]

3. Other evidence of the difficulty of sequencing DNA.

37. Between June and August of 1992, as Merck was in the process of trying to construct a working human COX-2 clone, it made and sequenced three human COX-2 clones.[67] One important part of cloning a new cDNA was sequencing the cDNA to "make sure that the nucleotides were correct."[68]

38. However, all three clones Merck had produced "were found to contain sequence errors introduced by the Taq polymerase during amplification."[69]

39. As Pfizer expert Dr. Mancini testified, it was known in the 1992 period that using "Taq polymerase" could give rise to errors, so "that's why usually what you did" was:

> obtained multiple clones to try and piece together the best sequence or the sequence that was consistent in several clones to feel comfortable.[70]

40. Similarly, in March 1993, when Monsanto was trying to construct human COX-1 and COX-2 clones, it asked a scientist named Joseph Polazzi to sequence a possible human COX-1 clone Monsanto had developed.[71]

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[66] *Id.*

[67] J. Mancini Dep., 7 Nov 11, Ex. 32 at 127:16-128:24.

[68] T. Hla Dep., *Univ. of Rochester v. Searle,* 16 Jan 03, 97:3-98:17, BYU-PFE 117667-782 at 692, Ex. 142.

[69] Merck Monthly Highlights, Aug 92, BYU-PFE189175-177 at 176, Ex. 129.

[70] J. Mancini Dep., 7 Nov 11, Ex. 32 at 128:7-24.

[71] *Id.* at 199:16-201:2.

41. The next month, in April 1993, Polazzi reported that one of his primers didn't work, so that, though "COX-1 sequencing [was] 95 percent complete," "[o]ne small gap in the primers gave no data."[72] As Pfizer expert Dr. Mancini testified, this was not unusual: "Sometimes you design primers, and they don't work," so you "have to redesign new primers."[73] Polazzi also reported that a "larger gap in the noncoding 3-prime end has not been confirmed," and "there are several locations where data from only one strand has been obtained."[74]

42. As Dr. Mancini testified, this doesn't necessarily mean that Polazzi wasn't doing the experiment right; rather, "It could have been he had trouble in different ways," because there are "many different ways" for problems to arise:

> It could be the primer itself. It could be he had trouble with the sequence or how he was doing the sequencing. It could have been trouble with the gel. **So there's many ways**.[75]

43. Nor were these type of problems unique to Polazzi. As Dr. Mancini acknowledged, "**These kinds of problems can crop up in sequencing**."[76]

44. As another example, in 1991, the mouse COX-2 cDNA sequence published by Dr. Harvey Herschman of UCLA differed by one amino acid from the protein described in a publication by University of Rochester scientist, Young, in a June 1992 publication.[77]

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[72] *Id.* at 202:3-204:25.
[73] *Id.* at 204:13-24.
[74] *Id.* at 205:1-16.
[75] *Id.* at 206:9-22.
[76] *Id.* at 206:24-207:4 (emphasis added).
[77] Second Decl. of D. Simmons, *Cromlish v. Young*, 20 Jan 01, Ex. 122 at pp. 5-6, BYU-09-1883-884.

D. DeWitt's 1990 Mouse COX-1 DNA Sequence Did Not Make a Mouse COX-1 cDNA Readily Available, Because Making A cDNA Clone In The Early 1990s Was Tedious, Difficult And Time Consuming.

1. By 1992, after working with BYU's confidential information, Monsanto realized it was in a race to be the first to market a COX-2 selective drug, so it changed its research focus and mobilized its scientists in an intense, highly-focused effort.

45. Prior to receiving Dr. Simmons's materials and information in April 1991, Monsanto was not looking for an improved non-steroid anti-inflammatory drug (NSAID), but was focusing on "steroid related research."[78] By 1992, however, having enjoyed the benefit of Dr. Simmons's materials and information for several months, Monsanto was pursuing its own "COX-2 project" searching for a COX-2 selective NSAID.[79] By that time, Monsanto realized it was in a "horse race" to be the first company to find and market a COX-2 selective drug.[80]

46. Monsanto understood that "in drug development, time really is money," and that "for each day that development is accelerated" on an average drug, "there is $1 million added to the company's sales figure.[81] However, Monsanto believe that, for Celebrex, "this figure could approach $10 million per day."[82]

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[78] P. Isakson Witness Statement, 23 Aug 99, ¶¶ 11-14, Ex. 99.

[79] *Id.* ¶¶ 31-33.

[80] Email exchange between P. Isakson and P. Needleman, 26 Jun 92, Needle-P 10000013898, Ex. 230; *cf.* Searle Memo to COX PLT Team from P. Isakson, 27 Oct 93, PFC00290820-829 at 823, Ex. 240 ("Gorczynski ended the meeting by reminding us we are in a race, but that we can win")

[81] P. Needleman, *From a Twinkle in the Eye to a Blockbuster Drug*, 1 May 01, Research – Technology Magazine, BYU-PFE 831913-916 at 914, Ex. 83.

[82] *Id.*

47. Monsanto thus "mobilized 50 molecular and cell biologists to clone and express the human genes for both forms of the enzyme…creating an intense, highly-focused effort."[83] As described below, despite this "intense, highly-focused effort, it took Monsanto more than a year to construct cDNA clones for human COX-1 and COX-2,

2. Monsanto's own difficulty at making human COX cDNAs using both a published sequence and actual human COX clones demonstrates the difficult nature of cloning.

48. In February 1992, Monsanto began the process of trying to construct human COX cDNA clones using the first method of cloning described above, by making a library of human cDNA from a cellular source, then using the screening process to identify the COX genes.[84]

49. In March 1992, Dr. Tim Hla, a scientist at the American Red Cross, made the sequence of his human COX-2 clone publicly available to the scientific community via the "globally accessible genetic database, Genbank."[85]

50. In May 1992, Dr. Seibert sent a letter to Dr. Tim Hla asking him to provide Monsanto with his human COX-1 and COX-2 clones for the purpose of Monsanto using them to generate its own human COX-1 and COX-2 clones.[86] As reflected in Dr. Seibert's letter, Monsanto understood that it was restricted from using Hla's clones themselves for drug

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[83] *Id.*

[84] J. Mancini Dep., 7 Nov 11, Ex. 32 at 188:12-189:2.

[85] Second Decl. of D. Simmons, *Cromlish v. Young*, 20 Jan 01, Ex. 122 at ¶ 7, BYU-09-1883-884.

[86] Ltr. to T. Hla from K. Seibert, 28 May 92, S00664130, Ex. 130.

development, but Monsanto could use Hla's clones to derive its own clones that would then be useful in Monsanto's drug development effort.[87]

51. On or around 13 July 1992, Monsanto received Dr. Hla's human COX-1 and COX-2 clones, and continued its efforts to develop and characterize its own set of human COX clones.[88]

52. Despite having Dr. Hla's published human COX-2 sequence, and having Dr. Hla's actual human COX-1 and COX-2 clones to use as probes, it was not until at least April 2003—thus, over a year from when it began in February 1992—that Monsanto had developed and sequenced a human COX-1 and COX-2 clone, and even then, as noted above, Monsanto still had some sequencing problems it was trying to work out.[89]

53. As even Pfizer expert Dr. Mancini admitted, it took "approximately a year" to obtain a human COX-1 and COX-2 clone, and that was so even though Monsanto had "published information about the DNA sequence of both human COX-1 and COX-2," and also had "actual clones in their possession."[90]

3. The actual experience of Merck and others confirm the difficulty of developing a cDNA clone.

54. Although the expert report of Pfizer expert Dr. Mancini states his opinion that, "under routine circumstances," the process from going from a sequence published in the

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[87] *Id.*

[88] K. Seibert Monsanto Notebook No. 4,956,601 at 675, 13 Jul 92, PFC01549824, Ex. 40.

[89] J. Mancini Dep., 7 Nov 11, Ex. 32 at 215:1-216:2.

[90] *Id.* at 214:4-216:2.

literature to obtaining an actual clone would take no more than two weeks to complete," he admitted that he never did it that fast himself in either 1991 or 1992.[91]

55. In fact, Dr. Mancini testified that a variety of things "can go wrong" when a scientist tries to construct a clone, including "PCR mistakes."[92] Another potential problem is the fact that some mRNA libraries can be "more difficult to generate," and even when you generate the library, you don't always get a "full length gene or a full-length cDNA" from a library, meaning you have to clone more than one library and then splice together the "fragments" that you get.[93]

56. In June 1992, Merck—the company for whom Dr. Mancini was then working—received Dr. Hla's nucleotide sequence for human COX-2, as published in GenBank, and began working on a human COX-2 clone.[94] As Dr. Mancini testified, it then took Merck at least six months, from June 1992 until at least December 1992, to construct, sequence and characterize the human COX-2 clone, and even as of December 1992, there remained questions as to whether Merck's human COX-2 clone had the correct sequence.[95]

57. Once Merck had cloned a human COX-2 cDNA, and characterized that clone, Merck learned that the sequence of its clone "was different than the published [Hla] sequence at amino acid position 165."[96] According to Dr. Mancini, this was a problem, because:

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[91] *Id.* at 168:22-169:16; 171:5-13.
[92] *Id.* at 238:21-240:21.
[93] *Id.*
[94] *Id.* at 122:17-123:8.
[95] *Id.* at 135:3-140:3.
[96] *Id.* at135:17-136:11.

> [A]t this time we were preparing to construct recombinant cell lines to express the proteins. We wanted to make sure we had the correct sequence for Cyclooxygenase-2 before we started using this for recombinant enzyme screening.[97]

58. As of December 1992—six months after Merck first began trying to construct a human COX-2 cDNA—Merck and its team of scientists was still trying to "determine what was the correct sequence," as a part of making sure its human COX-2 was "ready to go for appropriate use for drug screening,"[98]

59. According to Dr. Mancini, although Merck "could have had the COX-2 clone as early as the end of September [1992]," as of December of 1992, there "was still a question here whether there was a polymorphism."[99] (A polymorphism is a difference in the same gene between one person and another, and so not necessarily an error in the sequence.)[100]

60. Per Dr. Mancini, because "a lot of effort" was "going to be put into recombinant screens, recombinant purification of protein," Merck "**wanted to make sure we had the correct cyclooxygenase** moving forward."[101] And as of December 1992, Merck was "still working on that issue…"[102]

61. Dr. David A. Jones of the University of Utah has also testified that it took his lab "on the order of six to eight months" to develop a human COX-2 clone, which they completed

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[97] *Id.* at 137:9-20.
[98] *Id.* at 138:7-16; *see also* 140:21-146:17.
[99] *Id.* at 140:21-142:3.
[100] *Id.* at 139:4-16.
[101] *Id.* at 139:22-140:3.
[102] *Id.* at 139:17-21.

sometime in the fall of 1992, prior to 16 November 1992, the date his team published an article about that work.[103]

62. Another Pfizer expert, Dr. Hla, in a deposition taken years before this case, acknowledged that cloning and characterizing a gene was "absolutely" a "t edious task" that involved experiments that were both "tedious" and "difficult."[104] When asked how he would characterize such experiments, Dr. Hla testified:

> I would characterize them as intensive and—you know, it was a race, and it was—it was a risk, but something that we really wanted to succeed **and worked very hard at it** for quite a number—you know, **for quite some time** to succeed.[105]

4. <u>Merck considered its COX-2 cDNA to be a unique and valuable asset, even though a published cDNA sequence existed prior to Merck's development of its own cDNA</u>.

63. As Pfizer-expert Dr. Mancini testified, Merck considered the human COX-2 clone it had developed to be "unique":

> Q. And Merck would consider its human COX-2 sequence that it developed during this June period and forward to be a unique clone proprietary to Merck; correct?
>
> A. **It was a unique clone**.[106]

64. Merck would not have wanted to give its COX-2 clone out to competitors.[107] Merck felt its COX-2 clone was a "more active clone," and "if it had anything to do with binding inhibitors, it would be very important in selecting compounds."[108]

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[103] D. Jones Dep., *Cromlish v. Young,* 12 Feb 01, 48:9-50:3, UOR10-03349-350, Ex. 143.

[104] T. Hla Dep., *Univ. of Rochester v. Searle,* 16 Jan 03, Ex. 142 at 58:57:25-59:13; 97:3-99:12, BYU-PFE 117682, 692 (emphasis added).

[105] *Id.* at 59:3-13.

[106] J. Mancini Dep., 7 Nov 11, Ex. 32 at 147:7-11.

65. In fact, even though Dr. Hla had published the nucleotide sequence of human COX-2 in March 1992, in May 1993, C romlish and other Merck Frosst scientists filed an application with the U.S. Patent and Trademark Office ("USPTO") seeking to obtain a patent on a human COX-2 clone, and, in August 1996, the USPTO granted that patent, No. 5,543,297.[109]

66. The Merck '297 patent has data showing that its human COX-2 clone was 1.3 to 2.3 times more active than a human COX-2 clone using Dr. Hla's published nucleotide sequence.[110]

67. Pfizer expert Dr. Mancini also testified that Merck would not have shared its COX-1 and COX-2 cell lines with another company, even though the sequences were "publicly available," because, per Dr. Mancini:

- "we spent time developing them ourselves in-house";
- "we believed they were unique, that we had two cell lines that were unique within Merck and within the public domain," even though "the sequence was not unique" but "was in the public domain";
- "the identification that one was COX-2 selective and one was COX-1" was unique to Merck;
- "it took a significant amount of work" for Merck to develop them; and
- "we did spend some time characterizing those, and we felt that they were unique to Merck."[111]

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[107] *Id.* at 146:23-148:17.
[108] *Id.* at 148:5-17.
[109] Mem. Opinion and Order, 29 Mar 02, *Cromlish v. Young,* Ex. 127 at p. 3.
[110] J. Mancini Dep., 7 Nov 11, Ex. 32 at 154:19-156:18.
[111] *Id.* at 71:23-74:24.

68. In this lawsuit, Pfizer itself claims that, although Monsanto received an actual COX-2 clone from Dr. Simmons, and Monsanto didn't "know of any particular" defect in that clone,[112] Monsanto was not able to get it to express protein.[113]

E. Dr. Simmons's COX-1 Clone Was Different Than Dr. DeWitt's COX-1 Clone And Had A Different Nucleotide Sequence And Restriction Map Than DeWitt's.

69. Dr. Simmons began his own independent cloning of his mCOX-1 clone by first isolating a sheep COX-1 cDNA in 1990.[114] He then used this clone to screen a mouse cDNA library made for the purpose of cloning full-length cDNAs.[115] From this effort, he isolated his own mCOX-1 cDNA clone, which he then sequenced by approximately mid-January 1991.[116]

70. As Dr. Simmons stated in one of his expert reports in this case, the mouse COX-1 sequence published in Dr. DeWitt's 1990 paper

> was not the same as the mouse COX-1 DNA sequence that I provided to Monsanto, nor would the mouse COX-1 restriction map generated from that sequence be the same as the one I provided Monsanto. Because my cDNA was different, especially because it began and ended at different positions and was in a different vector, my restriction map was distinct from his and revealed specific features of my clones that would have been useful to those working with it, particularly those at Monsanto, including the orientation of the cDNA within the Bluescript vector.[117]

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[112] S. Hauser Dep., 27 Oct 10, 214:21-24, Ex. 37.

[113] Ltr. to E. Bramhall from D. Hoscheit, 17 Mar 00, BYU-12-0071-074, Ex. 131.

[114] D. Simmons Amended and Supp. Expert Rpt., 10 Jun 11, Ex. 57 at ¶ 259.

[115] *Id.* at ¶ 334.

[116] *Id.* ¶ 339-341.

[117] D. Simmons Rebuttal Expert Rpt., 26 Aug 11, Ex. 161 at ¶ 95.

71. BYU's expert Dr. Bell also testified that, although DeWitt's 1990 article described his construction of a mouse COX-1 clone, Dr. Simmons's COX-1 clone "was unique"; it "wasn't the same as the Dave DeWitt clone."[118] Specifically, Dr. Simmons's COX-1 clone had a different nucleotide sequence than Dr. DeWitt's.[119]

72. As Dr. Bell testified, Dr. Simmons's COX-1 clone was different "in the three-prime five-prime ends of the clone," so "it would have different restrictions maps, different ways of making vectors, et cetera."[120] And those differences affect "how you can handle it, the case of putting it into vectors."[121]

[118] R. Bell Dep., 29 Sep 11, Ex. 138 at 127:21-128:11.
[119] *Id.* at 128:14-22.
[120] *Id.*
[121] *Id.* at 129:1-8.

LEGAL ARGUMENT

I. SUMMARY JUDGMENT STANDARD.

"Summary judgment is a drastic remedy," and the Tenth Circuit cautions that "any relief pursuant to Fed.R.Civ.P. 56 should be awarded with care."[122] As that court stated: "Unless the moving party can demonstrate his entitlement beyond a reasonable doubt, summary judgment must be denied." *Id.* The court should "examine the record to determine if any genuine issue of material fact" is in dispute, and in doing so should "view the evidence and draw reasonable inferences therefrom in the light most favorable to the nonmoving party."[123]

"Trade-secret status is a question of fact," and if there are "doubts as to the existence of triable issue of fact," those doubts "must be resolved in favor of the existence of triable issues."[124]

II. DR. SIMMONS'S MOUSE COX-1 MATERIALS QUALIFIED AS TRADE SECRETS BECAUSE THEY WERE NEITHER GENERALLY KNOWN NOR READILY AVAILABLE TO MONSANTO.

A. Summary of Argument.

Under Utah's version of the Uniform Trade Secrets Act (the "UTSA"), a trade secret includes a "formula, pattern, compilation, program, device, method, technique, or process that derives independent economic value, actual or potential" from:

> not being **generally known** to, and not being **readily ascertainable** by proper means…"[125]

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[122] *Conaway v. Smith*, 853 F.2d 789, 792 n. 4 (10th Cir.1988).

[123] *Byers v. City of Albuquerque*, 150 F.3d 1271, 1274 (10th Cir. 1998).

[124] *Harvey Barnett, Inc. v. Shidler,* 338 F.3d 1125, 1129 (10th Cir. 2003).

Pfizer's motion does not dispute that BYU's COX-1 materials had independent economic value to Monsanto, and the facts show that Monsanto used Dr. Simmons's mouse COX-1 cDNA in its research leading to Celebrex.[126] Rather, Pfizer argues that BYU's COX-1 materials weren't trade secrets because they had allegedly been "publicly available for more than one year" before BYU provided them to Monsanto. But BYU has produced overwhelming evidence—including admissions from Pfizer's own witnesses—refuting that argument, or certainly raising genuine issues of fact for trial on the matter.

BYU's evidence includes the admission of Monsanto's Dr. Seibert that, in Monsanto's COX-related research, it used only Dr. Simmons's mouse COX-1 cDNA clone, that Dr. Simmons's clone was "useful," and that she knew of "no other" source for such in either 1991, 1992 or 1993.[127] And courts have uniformly held that when defendants have actually used a plaintiff's confidential material, it is no defense for the defendants to later argue that they "could have" obtained the material from some public source: "The fact is that they did not."[128]

Pfizer's argument about the supposed "public availability" of BYU's mouse COX-1 materials in 1991 relies on a 1990 article published by a Michigan State University scientist, Dr. David DeWitt, in which he says that his lab cloned (what would today be called) a mouse COX-1 clone; the article also sets forth the nucleotide and amino acid sequence of his clone, along with a

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[125] UCA § 13-24-2(4)(a). The statute also requires "efforts that are reasonable under the circumstances to maintain [the trade secret's] secrecy," but Pfizer's motion does not address that issue.

[126] SOF ¶¶ 12-14.

[127] SOF ¶¶ 12-17.

[128] *E.g. Franke v. Wiltschek,* 209 F.2d 493, 495 (2d Cir. 1953)

"restriction map" of his clone.[129] But plain common sense suggests—and the evidence shows—that there is a huge difference between a magazine article listing row upon row of DNA sequences, and someone handing you a test tube containing an actual COX-1 cDNA organism.

The facts set forth above show that in the early 1990s, producing an accurate biological cDNA clone based just on a DNA sequence was a tedious, difficult, lengthy process, "fraught with error."[130] Monsanto has a direct appreciation for that, because—despite having mobilized 50 molecular and cell biologists—it struggled for over a year to construct a human COX-2 cDNA clone, even though the human COX-2 DNA sequence had been previously published.[131]

BYU has also adduced facts showing that the DNA sequence for Dr. Simmons's mCOX-1 cDNA differed from that of Dr. DeWitt's at the 3' and 5' prime ends, and that Dr. Simmons's restriction map was also different in important ways.[132]

B. In 1991, BYU's COX-1 Materials Were Not "Generally Known"; In Fact, Dr. Simmons Was Monsanto's Only Known Source.

Monsanto's Dr. Seibert made two key admissions in her deposition: first, that the only mouse COX-1 clone Monsanto ever used was the one she received from Dr. Simmons on 29 April 1991, and second, that from 1991 to 1993, she was unaware of any "publicly-available source" for a mouse COX-1 cDNA.[133] By themselves, these twin admissions suffice to raise a

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[129] In 1990, Dr. Simmons's 1989 discovery of a separate COX-2 clone had not yet been publicly announced, so Dr. DeWitt referred to his mouse COX construct as, mouse "PGG/H synthase," not "COX-1."

[130] SOF ¶¶ 19-62.

[131] SOF ¶¶ 45-53.

[132] SOF ¶¶ 8, 69-72.

[133] SOF ¶¶ 12-14.

fact issue as whether Dr. Simmons's mouse COX-1 clone was "generally known" within the meaning of the statute.

And Dr. Seibert's testimony was buttressed by the admissions of Pfizer's expert, Dr. Mancini, who admitted that the only other source of mCOX-1 he could recall in the 1991 to 1993 time period was Dr. DeWitt, and Mancini had "no idea" whether Dr. DeWitt would have given that clone out to anyone.[134] Indeed, Dr. Mancini candidly admitted that he didn't think Merck ever shared its COX "clones or other reagents" with its competitors, whether or not published sequences existed for them.[135]

As for the related COX-1 DNA sequences and restriction maps, Dr. Simmons testified that the mouse COX sequence published in DeWitt's 1990 paper "was not the same as the mouse COX-1 DNA sequence that I provided to Monsanto, nor would the mouse COX-1 restriction map generated from that sequence be the same as the one I provided Monsanto."[136] Moreover, Dr. Simmons said, because his cDNA was different, "my restriction map was distinct from [Dr. DeWitt's] and revealed specific features of my clones that would have been useful to those working with it, particularly those at Monsanto, including the orientation of the cDNA within the Bluescript vector."[137]

And BYU expert Dr. Bell also testified that Dr. Simmons's COX-1 clone was "unique" and "wasn't the same as the Dave DeWitt clone," and had a different nucleotide sequence than

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[134] SOF ¶ 15.
[135] SOF ¶ 16.
[136] SOF ¶ 70.
[137] *Id.*

Dr. DeWitt's.[138] Specifically, Dr. Simmons's COX-1 clone differed from DeWitt's "in the three-prime five-prime ends of the clone"; hence, it "would have different restrictions maps, different ways of making vectors, et cetera," and those differences would affect "how you can handle it, the case of putting it into vectors."[139] At a minimum, this evidence suffices to raise a genuine issue of fact on whether BYU's COX-1 materials were generally known in 1991.

C. In 1991, BYU's COX-1 Materials Were Not "Readily Ascertainable By Proper Means."

1. Making a c DNA clone was a lengthy and difficult process that required a combination of skill and information.

Pfizer argues that, since the "*steps and techniques*" for obtaining a clone based on a known DNA sequence were publicly available, that means the *actual* COX-1 cDNA clone had no "independent economic value" and hence was not a trade secret. Pfizer Mem. at 4-5. But that's rather like saying that an actual atomic bomb has no more value than does information on the Internet about the "steps and techniques" for making such.

In fact, and as described in the statement of facts above, making and sequencing a cDNA clone in the early 1990s was, like other biological constructs, a lengthy and difficult process that was "fraught with error."[140] And the best evidence of that comes from the time it actually took scientists in the 1990s to construct such clones, including Pfizer-predecessor Monsanto (over a year),[141] and its chief competitor, Merck (at least six months).[142]

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[138] SOF ¶ 71.
[139] SOF ¶ 71-72.
[140] SOF ¶¶ 24, 33.
[141] SOF ¶¶ 48-53.
[142] SOF ¶¶ 54-60.

Monsanto's own experience is the most probative, because Monsanto—understanding that it was in a "race" to successfully develop a COX-2 selective NSAID, and that each day saved was potentially worth $10 million—"mobilized 50 molecular and cell biologists to clone and express the human genes for both forms of the [COX] enzyme," thus "creating an intense, highly-focused effort."[143] Yet it still took Monsanto over a year to accomplish that task. Using Monsanto's own "$10 million a day" metric, the fact that Monsanto didn't need to spend any time developing a *mouse COX-1 clone* had enormous economic value to Monsanto.

Similarly, it took Dr. David Jones at the University of Utah "on the order of six to eight months" to develop a human COX-2 clone, which his team completed in the fall of 1992.[144] And even Pfizer expert Dr. Hla, in a deposition taken years before this case, admitted that cloning and characterizing a gene was "absolutely" a "tedious task" that involved experiments that were both "tedious" and "difficult."[145] And Dr. Hla further testified that he "worked very hard at it" for "quite some time" before succeeding.[146]

An actual cDNA clone is really the final embodiment of a compilation of scientific information, materials, knowledge and skill. That is evident from reading Dr. DeWitt's article, and is equally evident from the actual experience of Merck and Monsanto, as well as Drs. Tim Hla and David Jones related above. Hence, by itself, a cDNA clone is a compilation trade secret that—though based in part on publicly-available information and materials—constitutes a unique integration of that information based on the skill and expertise of a scientist.

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[143] SOF ¶¶ 45-47.
[144] SOF ¶ 61.
[145] SOF ¶ 62.
[146] *Id.*

On these facts, a jury could surely conclude that having Dr. Simmons's mouse COX-1 cDNA in hand was a valuable asset that gave Monsanto an economic advantage over other companies that had to construct their own clones based on published steps and techniques. Dr. Simmons's mCOX-1 cDNA clone was thus a trade secret.

2. Under pertinent case law, a jury could conclude that BYU's COX-1 materials were not readily ascertainable because of the time, effort and expense that Monsanto would have needed to reproduce such materials.

Under the UTSA, a trade secret:

> may include a grouping in which the components are in the public domain but there has been accomplished **an effective, successful and valuable integration** of those public elements such that the **owner derives a competitive advantage** from it.[147]

Also under UTSA, materials can be trade secrets if they are not "readily ascertainable by proper means."[148] And although what is "readily ascertainable" for trade secret purposes is "an intensely factual inquiry" in each case,[149] some general principles confirm that a jury could find, on the facts here, that BYU's COX-1 materials were not "readily ascertainable."

One of the factors courts examine is "the ease or difficulty with which the information could be properly acquired or duplicated by others."[150] "A secret may not be in the public domain if extensive effort is required to pierce its veil by assembling the literature concerning it

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[147] *USA Power, LLC v. PacifiCorp,* 235 P.3d 749, 759, ¶ 43 (Utah 2010), *quoting, Enter. Leasing Co. v. Ehmke*, 3 P.3d 1064, 1069, ¶ 17 (Ariz. App. 1999).
[148] UCA § 13-24-2(4)(a).
[149] *USA Power, LLC v. PacifiCorp,* 235 P.3d 749, 760 ¶ 45 (Utah 2010).
[150] *Id.*

and thereby uncover its parts."[151] The facts set forth above show that constructing a cDNA clone based on publ icly-available materials required extensive effort, and was difficult, not easy. Moreover, a "compilation need only be **a slight advance over common knowledge** to receive protection."[152]

In *Amoco Production Co. v. Laird,* Indiana's Supreme Court addressed the meaning of the phrase "not being readily ascertainable," as used in Indiana's version of the UTSA.[153] That case involved an oil company, Amoco, that spent several months with a team of experts trying to determine the oil reserve potential of an area in the Northeast Central United States. After a variety of research—including paying a company $150,000 to conduct an aerial microwave radar survey—the team eventually focused on a 13,000-square-mile area known as the Trenton Black River formation. But after Amoco then decided not to pursue any exploration at that time, one of its employees sent a map showing the determined oil field locales to a friend, William Laird, who promptly started obtaining oil and gas exploration leases in the area. When Amoco discovered this, it sued Laird, claiming among other things, a misappropriation of trade secrets.

Laird argued that—even though he *actually* used his friend's map as a guide to obtaining the leases—it would have been "economically feasible" for him to have identified the oil fields by other, publicly-available means, and Amoco hadn't shown otherwise. For its part, Amoco argued that Laird could only have located the oil fields "by considerable expenditure of time,

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[151] *Microbiological Research Corp. v. Muna,* 625 P.2d 690, 696 (Utah 1981), *quoting* 2 Callman, *Unfair Competition, Trademarks and Monopolies* (3red Ed., Sec. 51.1, pp. 391-392).

[152] *Enter. Leasing Co. v. Ehmke*, 3 P .3d 1064, 1 070, ¶ 19 (Ariz. Ct. App. 1999) (emphasis added).

[153] 622 N.E. 2d 912, 913 (Ind. 1993)

effort, and expense," hence, the information was not "readily ascertainable." Although the trial court agreed with Amoco, the court of appeals reversed, holding that since Laird could have generated the information on his own—even though it would be "more expensive and difficult"—the information was not a trade secret.[154]

On review, Indiana's Supreme Court overruled the court of appeals and affirmed the trial court, holding that a defendant's "economic capacity to obtain information by other proper means" is "a notion extraneous" to the UTSA and Indiana's version of it.[155] The court said:

> We thus find that, consistent with the interpretation of the UTSA in other jurisdictions, where the duplication or acquisition of alleged trade secret information requires a **substantial investment of time, expense, or effort**, such information may be found "not being readily ascertainable" so as to qualify for protection under the Indiana Uniform Trade Secrets Act.[156]

Moreover, the court also offered this trenchant observation:

> Even if information potentially could have been duplicated by other proper means, **it is "no defense to claim that one's product could have been developed independently** of plaintiff's, if in fact it was developed by using plaintiff's proprietary designs."[157]

D. Because Monsanto Admittedly Used Dr. Simmons's COX-1 Materials, It Can't Now Claim That It Could Have Developed The Materials Independently.

As many courts have held, when a defendant actually uses a plaintiff's confidential information to gain an advantage, it can't later defend that use on the ground that it "could have" developed the information itself. The Second Circuit discussed this issue in *Franke v. Wiltschek,*

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[154] *Laird v. Amoco Prod. Co.,* 604 N.E. 2d 1249 (Ind. App. 1992).

[155] *Amoco Prod. Co. v. Laird,* 622 N.E.2d 912, 917 (Ind. 1993).

[156] *Id.,* 622 N.E.2d at 919 (emphasis added).

[157] *Id.,* 622 N.E.2d at 918 (emphasis added), *quoting Televation Comm. Sys. Inc. v. Saindon,* 522 N.E.2d 1359, 1365 (Ill App. 1988).

where the defendants, through subterfuge, gained access to plaintiffs' proprietary information about its compressed cotton bath sponges, then started their own competing business.[158] The defendants then argued that the "heart of the process" for making the sponges was publicly available, through an expired patent: the court rejected the argument, however:

> **It matters not that defendants could have gained their knowledge from a study of the expired patent** and plaintiffs' publicly marketed product. **The fact is that they did not**. Instead they gained it from plaintiffs via their confidential relationship, and in so doing incurred a duty not to use it to plaintiffs' detriment.[159]

In *Merck & Co., Inc. v. SmithKline Beecham Pharms. Co.,* Delaware's court of chancery applied the same principle in a trade secret case involving a complex process for making a chicken pox vaccine.[160] In finding that SmithKline Beecham had misappropriated a compilation trade secret relating to the vaccine, the court observed that, the "mere fact that aspects of a trade secret process can be found in publications does not mean that the process is not a trade secret."[161] "For this reason," the court said, "courts have rejected the argument that one who has learned particular information from a trade secret process is not liable if it can show that the information learned is somewhere 'published.'"[162] The court went on to state:

> SB [SmithKline Beecham] has not cited any case in which a court has allowed what SB has done—gained valuable information from

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[158] 209 F.2d 493 (2d Cir. 1953).

[159] *Id.,* 209 F.2d at 495 (emphasis added).

[160] 1999 Del. Ch. LEXIS 242, *affirmed, SmithKline Beecham Pharm. Co. v. Merck & Co.,* 746 A.2d 442 (Del. 2000).

[161] *Id.* at *55.

[162] *Id.*

> access to a trade secret process and attempted to avoid liability by pointing to some publication of the particular information used.[163]

In its holding on this matter, the *Merck* court relied in part on two other cases, *Rohm and Haas Co. v. Adco Chem. Co.,*[164] and *Monovis, Inc. v. Aquino.*[165]

In the *Rohm and Haas* case, the plaintiff had, over a several year period, come up with an improved process for making latex paint. Though other companies tried to offer competitive products, only one company succeeded in doing so, and then only after hiring a former Rohm and Haas employee, Ron Harvey. At trial the defendants asserted that the manufacturing process could be found in various publications, but it was not disputed that the defendants *in fact* received the process from Harvey, and that Harvey had not consulted those publications; he had simply drawn upon knowledge gained from his work at Rohm and Haas. Based on such facts, the court found "no reason to suspect that the defendants could have duplicated the Process through skill and effort using the available literature."[166] Thus, the Third Circuit reversed the district court and found that the manufacturing process was a trade secret.

Here, there is no evidence that either Dr. Seibert or anyone else at Monsanto ever consulted Dr. DeWitt's 1990 a rticle or tried themselves to make a mouse COX-1 clone. Monsanto simply took Dr. Simmons's clone, used it for its benefit in direct violation of Research Agreement paragraph 4.1, and now in essence argues that it could have theoretically made its own COX-1 if it wanted. This is very similar to the argument the *Monovis* court soundly

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[163] *Id.* at *59.
[164] 689 F.2d 424 (3d Cir. 1982).
[165] 905 F. Supp. 1205 (W.D.N.Y. 1994).
[166] Rohm & Haas, 689 F.2d at 431.

rejected. There, the defendants argued that, "if they can presently reconstruct the plaintiffs' trade secrets from public information upon which they theoretically could have relied," then the information was not a trade secret.[167] But the court ruled otherwise, finding such an argument was "not the nature of trade secret law."

And on the demonstrated facts here, when Monsanto actually tried to make its own human COX clone, it took its team of 50 molecular and cell biologists a full year to do so—proving perhaps better than anything that constructing a COX clone was indeed difficult and time consuming.

Most recently, the Eighth Circuit Court of Appeals in *AvidAir Helicopter* has reiterated this same principle, finding that, under the UTSA, the "fact that information can be ultimately discerned by others" does not make it unprotectable, quoting with approval from *Laird, supra,* that "it is no defense to claim that one's product could have been developed independently of plaintiff's, if in fact it was developed by using plaintiff's proprietary designs."[168]

E. Biological Constructs Are By Nature Unique And Proprietary.

The science of creating organisms that can be precisely replicated or "cloned" involves complex molecular concepts and techniques, so when a company successfully integrates its skill and knowledge to make such a construct, the result is considered unique and proprietary. For example, as Pfizer's own expert, Dr. Mancini, testified, Merck would not have shared its COX-1 and COX-2 cell lines with another company, even though the sequences were "publicly available," because, per Dr. Mancini:

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[167] *Monovis Inc. v. Aquino,* 905 F. Supp. 1205, 1227 (W.D.N.Y. 1994)

[168] *AvidAir Helicopter Supply, Inc. v. Rolls0Royce Corp.,* 2011 U.S App. LEXIS 24620 (8th Cir. Dec. 13, 2011).

- "we spent time developing them ourselves in-house";
- "we believed they were unique, that we had two cell lines that were unique within Merck and within the public domain," even though "the sequence was not unique" but "was in the public domain";
- "the identification that one was COX-2 selective and one was COX-1" was unique to Merck;
- "we did spend some time characterizing those, and we felt that they were unique to Merck;
- "it took a significant amount of work" for Merck to develop them.[169]

Both the uniqueness and technical difficulty of making molecular organisms are evidenced by the common happening of different scientists arriving at different DNA sequences for the same gene. As set forth above, two notable examples of this involved Dr. DeWitt himself. In 1988, Dr. DeWitt's published sequence of a sheep COX-1 differed from the sequence reported by another lab.[170] And in 1990, D eWitt, Pfizer-expert Dr. Hla, and five other scientists, published a paper noting 12 differences between Dr. Hla's human COX clone sequence, and the published sequence as reported in the GenBank database.[171]

Such incidents highlight the complexities of molecular biology, and science generally, but also illustrate a basic point: the fact that one scientist, in this case Dr. DeWitt, has published an article about something (here, a COX-1 cDNA sequence) does not mean that is the last word on the subject, or that what DeWitt said should now be accepted by all as scientific "public knowledge." It takes many repeat experiments before scientists are satisfied that they have

[169] SOF ¶ 67.
[170] SOF ¶ 26.
[171] SOF ¶ 27.

reached the right result.[172] That's why pharmaceutical companies do their own experiments and testing, and don't just accept what another scientist has written.

The Merck/University of Rochester patent dispute discussed above also underscores the uniqueness of biological constructs. There, Merck actually succeeded in getting a patent on the human COX-2 DNA sequence, even though there were other published versions of the sequence that were different.[173] The Board of Patent appeals eventually ruled in favor of Merck, making this specific finding:

> We find the testimony of Daniel L. Simmons on behalf of party Cromlish that obtaining the correct cDNA sequence (and amino acid sequence) encoding human COX-2 is fraught with difficulty to be highly credible."[174]

The Board then "decline[d] to assume" that some published sequences had been "accepted as the correct" sequences.[175]

CONCLUSION

For all the reasons advanced above, the Court should find there are, at a minimum, genuine issues of fact for trial, and should therefore deny summary judgment on Pfizer's motion.

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[172] As science philosopher Karl Popper wrote, "The demand for scientific objectivity makes it inevitable that every scientific statement must remain tentative for ever." *The Logic of Scientific Discovery* (1959).

[173] SOF ¶ 29.

[174] SOF ¶ 33.

[175] SOF ¶¶ 34-36.

RESPECTFULLY SUBMITTED this 22nd day of December, 2011.

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CERTIFICATE OF SERVICE

I hereby certify that on the 22nd day of December, 2011, I electronically filed the foregoing ***Response In Opposition To Defendants' Motion For Partial Summary Judgment Regarding Plaintiffs' Cox-1 Trade Secret Claims*** with the Clerk of the United States District, District of Utah Central Division, using the CM/ECF system which sent notification of such filing to the following:

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